REMARKS

By an Office Action dated July 1, 2002 in the file of the above-identified patent application, the Examiner in charge of this application rejected all the pending claims of the application based on a single prior art rejection. By this response, the applicant is responding to that ground of rejection. Reconsideration of the merits of this patent application is respectfully requested in view of this submission.

The first objection in the Office Action was to the specification. This objection related to the use of the trademark KnockOut SR. In each instance where the term is used in the specification, the term is capitalized and a generic term, i.e. "medium adjuvant" has been added to the specification. It is believed the usage of this term is now in compliance with the applicable rules.

The other remaining issue in the prosecution of this application was a rejection under 35 U.S.C. §103 over three prior art documents. The applicant continues to believe that the claims are not obvious over the cited prior art and makes arguments herewith to support that belief.

First, while the applicant has amended the claim language, this amendment was done for clarification and emphasis only, and neither expands nor contracts the scope of the claims. The language of "exogenously supplied" in referring to added fibroblast growth factor, is contained in the specification at page 8, line 3, and thus there is antecedent basis for this limitation. The changes to the claims were made to emphasize the fact that the claims recite a fibroblast growth factor is added to the medium in which the stem cells are cultured in accordance with the present invention. That fact seems to have been overlooked in the Office Action.

The Examiner agrees, in the Office Action, that methods used to isolate embryonic stem cells differ from species to species. The Examiner argues, however, that "once the cells are isolated, the means to culture said embryonic cells are very similar and pliant to various conditions, using feeder cells and growth factors from different species." While this broad statement may be true in general, it is important to note that not every culture condition or culture requirement translates precisely from species to species. Nor does every set of media and added proteins work equally efficiently with stem cells of differing species.

Note that the serum replacement adjuvant used by the inventor here was specifically developed to substitute for serum in the cultivation of murine embryonic stem cells. See, for example, the abstract of PCT WO 98/30679. If one refers to the examples contained in that

published PCT application, and actual research data contained in the Goldsborough paper, it is apparent that the medium was optimized for use with mouse embryonic stem cells. Yet that same medium is clearly not optimized for use with human embryonic stem cells, as the data in the present patent application make clear.

Note that the data contained in this patent application, and specifically the data contained at the bottom of page 7 of the specification of this patent application, demonstrate that exogenously added fibroblast growth factor has a synergistic effect in enhancing the growth and survivability of human embryonic stem cells in culture. Serum replacement with added fibroblast growth factor is a better medium than just the serum replacement alone. There is no suggestion in Goldsborough, or in any of the other art cited by the Examiner, of this significant difference in the culture requirements of human embryonic stem cells as contrasted to mouse embryonic stem cells.

The two cited patents to Hogan are no different. While their specification discusses what are purported to be embryonic stem cells from a variety of species, the only working examples contained in the application are with mouse cells. Neither Hogan patent provides any actual data to demonstrate that any particular medium is more useful or more efficient in cultivating human embryonic stem cells as opposed to mouse cells. Hogan et al. simply has no actual experimental data in its specification on actually culturing human stem cells.

The Examiner's rejection is based on the fact that Goldsborough teaches that a serum replacement is an obvious expedient for the cultivation of embryonic stem cells and therefore cultivating them in a serum free medium is not patentable. However, Goldsborough does not teach a requirement for, and does not teach that any benefit can be obtained from, the addition of a fibroblast growth factor to the medium. Accordingly, the art relied by the Examiner does not make obvious the claims of this application, which specifically recite the addition of a fibroblast growth factor to the serum free medium in which primate embryonic stem cells are cultivated. The addition of this factor adds to the efficient cultivation of these cells and is not in any way made obvious or suggested by any of the prior art references. Accordingly, these references cannot make obvious the claims of the present invention.

Accordingly, it is respectfully requested that the merits of this patent application be revisited once again.

Lastly, enclosed with this response is a Form PTO-1449 and a copy of published US Patent Application 20020081724. This application was apparently filed January 11, 2000, and may be prior art under 35 U.S.C. §102(e) if it issues as a patent. The use of basic

fibroblast growth factor in media for stem cell culture is mentioned at several points, e.g. page 22, paragraph 0130 and page 43, paragraph 0260. This disclosure is made only out of an abundance of caution.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Applicant: James A. Thomson

Serial No.: 09/522,030

Filed: 03/09/2000

For: SERUM FREE CULTIVATION OF PRIMATE EMBRYONIC STEM CELLS

Date: December 2, 2002

Group Art Unit: 1632

Examiner: J. Woitach

File No.: 960296.96544

In the Specification

Page 6, delete the paragraph beginning on line 3 and substitute the following:

Techniques for the initial derivation, culture, and characterization of the human ES cell line H9 were described in J. Thomson et al., 282 Science 1145-1147 (1998). In my experiments herein human ES cells were then plated on irradiated (35 gray gamma irradiation) mouse embryonic fibroblast. Culture medium for the present work consisted of 80% "KnockOut" Dulbeco's modified Eagle's medium (DMEM) (Gibco BRL, Rockville, MD), 1 mM L-Glutamine, 0.1 mM -mercaptoethanol, and 1% nonessential amino acids stock (Gibco BRL, Rockville, MD), supplemented with either 20% fetal bovine serum (HyClone, Logan, UT) or 20% KnockOut SR medium adjuvant, a serum-free replacement originally optimized for mouse ES cells (Gibco BRL, Rockville, MD). The components of KnockOut SR medium adjuvant are those described for serum replacements in W0 98/30679.

Page 6, delete the paragraph beginning on line 19 and substitute the following:

In alternative experiments medium was supplemented with either serum or the aforesaid serum replacer KnockOut SR medium adjuvant, and either with or without human recombinant basic fibroblast growth factor (bFGF, 4 ng/ml). The preferred concentration range of bFGF in the culture is between .1 ng/ml to 500 ng/ml.

In the Claims

Please amend Claims 1, 9, 14, and 17 as follows:

1. (Twice Amended) A method of culturing primate embryonic stem cells, comprising:

culturing the primate embryonic stem cells in a culture essentially free of mammalian fetal serum and [in the presence of] that contains exogenously supplied mammalian fibroblast

growth factor that is supplied from a source other than just a fibroblast feeder layer.

9. (Amended) A method of culturing primate embryonic stem cells, comprising:

culturing the stem cells in a culture essentially free of mammalian fetal serum and in the presence of a growth factor capable of activating a fibroblast growth factor signaling receptor, wherein the growth factor is exogenously supplied to the culture from a source other than just a fibroblast feeder layer.

14. (Amended) A culture system for culturing primate embryonic stem cells, comprising:

a fibroblast feeder layer; and

fibroblast growth factor exogenously supplied to the culture by other than just the fibroblast layer;

wherein the culture system is [essentially] free of added animal serum.

17. (Amended) A method of culturing primate embryonic stem cells, comprising:

culturing the primate embryonic stem cells in a culture free of added mammalian fetal serum and in the presence of fibroblast growth factor that is exogenously supplied to the culture from a source other than just a fibroblast feeder layer.

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